New findings with old drugs for osteoporosis

Evaluation of Cummings SR, Ettinger B, Delmas PD, et al. The effects of tibolone in old postmenopausal women. N Engl J Med 2008;359:697-708, and of Roux C, Fechtenbaum J, Kolta S, et al. Strontium ranelate reduces the risk of vertebral fracture in young postmenopausal women with severe osteoporosis.

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1. Introduction

Osteoporosis is the most common bone disease. Osteoporosis (porous bone, thinning of bone) affects > 10 million people in the US, including 2 million men, at an annual cost of US$17 billion [1]. It is associated with low bone mass (low bone mineral density) leading to stooped posture, loss of height, back pain and fractures. Nearly 2 million hip fractures occur each year in the US as a result of osteoporosis [1]. After hospital discharge, one in five people die in one year of hip fracture, and one in three require residential care placement [1].

Tibolone and strontium are both relatively old drugs that have recently been trialled for the treatment of postmenopausal osteoporosis. Tibolone has a combination of estrogenic, androgenic and progestogenic properties and was developed to alleviate menopausal symptoms. It has been suggested that when tibolone 2.5 mg is used as hormone replacement therapy, it may increase the incidence of breast cancer [2], although this has recently been disputed [3]. As tibolone is estrogenic, it also increases bone mineral density, and a low dose (1.25 mg) is being developed for the treatment of postmenopausal osteoporosis, and this development is discussed in Section 2.

Strontium is chemically similar to calcium, and can replace calcium in bone to strengthen it. In the 1950s, strontium-90 became famous as a dangerous, radioactive component of nuclear fallout produced during atmospheric testing of nuclear weapons, and this tarnished the reputation of strontium and stopped any development of strontium for the treatment of osteoporosis [4]. Recently, the development of strontium has been renewed with the making of strontium ranelate, which is ranelic acid with two atoms of stable non-radioactive strontium. Strontium ranelate is being developed for the treatment of postmenopausal osteoporosis and this is discussed in Section 3.

2. Tibolone

2.1 Introduction

Tibolone 1.25 mg/day has a similar ability to increase bone mineral density over 2 years in postmenopausal women with osteoporosis as tibolone 2.5 mg/day [5]. The most important studies in osteoporosis are those that determine whether increases in bone mineral density translate into reduced fractures, and this has been undertaken with tibolone in the Long-Term Intervention of Fractures with Tibolone (LIFT) clinical trial.

2.2 Methods and results

The methods and results of the LIFT trial showing that tibolone decreases the risk of fractures [6] are combined in this section. LIFT enrolled women aged 60 – 85 years with a T-score of-2.5 or less at the hip or lumbar spine, or a bone mineral density T-score of -2.0 with radiologic evidence of a vertebral fracture. Women with severe osteoporosis (T score of < -4) or clinical vertebral fracture were excluded, as were women with recent cancer or thromboembolic disease. Women using drugs with some similarity to tibolone (raloxifene or tamoxifen), or having recently used a bisphosphonate, were also excluded. Women with a uterus showing endometrial thickening (> 4 mm) were also excluded.

The 4534 enrolled women had a mean age of 68 years, with T scores of -1.8 at total hip and -2.9 at lumbar spine, and ~27% had existing vertebral fractures, and ~22% had a previous non-vertebral

fracture. All the enrolled women were taking 2 – 4 tablets of calcium with vitamin D (315 mg of calcium citrate with 200 IU of vitamin D_3) and were randomised to placebo or tibolone 1.25 mg.

The Data and Safety Monitoring Board reviewed unblended data every 6 months, and intervened in the study twice; initially, to notify the sponsor of a potential increased risk of stroke in the tibolone group, which the sponsor notified the women of, and 496 discontinued the study. About 6 months later, the board stopped the trial when the increased risk of stroke with tibolone had become definite, and tibolone had also been shown to decrease the risk of fractures.

When the trial was stopped after 34 months, 91% of the women had received ≥ 80% of scheduled doses. Vertebral fractures were assessed at baseline on a scale of 0 – 3, and during the trial an incident fracture was defined as a change of 1 on the scale with confirmation of fracture by radiologist, or by a decrease in vertebral height of 20% or more and 4 mm or more. Vertebral fractures occurred in 126 of 2257 women in the placebo group and this was reduced to 70 of 2249 women in the tibolone group. Non-vertebral fractures were confirmed by a radiologist or an orthopaedic surgeon. There were 166 in the placebo group, and this was reduced to 122 in the tibolone group. Tibolone increased bone mineral density in the spine and femoral neck by 4.8 and 3.1%, respectively.

Tibolone reduced the incidence of breast cancer (placebo, 19 cases; tibolone, 6) and colon cancer (placebo, 13; tibolone, 4). Tibolone had no significant effect on the incidence of coronary heart disease (placebo, 20; tibolone, 27) or venous thromboembolism (placebo, 9; tibolone, 3) but increased the incidence of stroke (placebo, 13; tibolone, 28).

There were no cases of endometrial cancer in the placebo group of 1773 women with a uterus but this cancer occurred in 4 of 1746 in the tibolone group ($p = 0.06$). Endometrial thickening of > 4 mm was more common in the tibolone group (533) than in the placebo group (168), as was vaginal bleeding (placebo, 2.5%; tibolone, 9.5%). Although the rates of moderate or severe dysplasia observed after cervical cytologic smear were low (≤ 0.4%) in both groups, the incidence of mild dysplasia or atypical cells of unknown significance was higher in the tibolone group (7.6%) than in the placebo group (3.2%).

2.3 Discussion

The reduction in relative risk of vertebral fractures was similar with tibolone as with estrogen, raloxifene and bisphosphonates, and the reduction of relative risk on non-vertebral fractures with tibolone was similar to estrogen [6].

The difference in absolute risk of stroke was higher in the ≥ 70 year olds (3.1 per 1000 person years) than in the 60 – 69 year olds (1.8 per 1000 person years). Thus, the authors concluded that tibolone should not be used on elderly women or women with risk factors for stroke [6].

3. Strontium ranelate

3.1 SOTI: the story so far

In 2004, the initial findings of the Phase III Spinal Osteoporosis Therapeutic Intervention (SOTI) trial of strontium ranelate in 1649 women with postmenopausal osteoporosis and one vertebral fracture, receiving calcium and vitamin D, were published [7]. After 1 year, the incidence of new fractures was lower in the strontium ranelate (2 g) group (6.4%) than in the placebo group (12.2%) [7]. After 3 years, 20.9% in the strontium group had a new vertebral fracture and this was less than in the placebo group [7]. Recently, it was shown that strontium ranelate improved the quality of life in these postmenopausal women [8].

The results of SOTI have been combined with those of another major Phase III clinical trial with strontium ranelate: the Treatment of Peripheral Osteoporosis study [9]. This increased the pool of women with postmenopausal osteoporosis and one vertebral fracture to 5082 [10]. In the first combination, strontium ranelate was shown to reduce the number of vertebral fractures over 3 years from 23.7% in the placebo group to 15.0% in the strontium ranelate group [10]. Non-vertebral

fractures were also reduced to a small extent in the strontium ranelate group (11.6%), compared to 13.1% in the placebo group [10]. In the most recent combination, data for the 2714 women who continued the studies for 5 years was presented, and showed that the incidence of non-vertebral fractures was 20.9% in the placebo group and reduced to 18.6% in the strontium ranelate group [11]. In the 1128 subjects at high risk of fractures (≥ 74 years, T score of ≤ -2.4), the incidence of hip fractures was lower in the strontium ranelate group (7.2%) than in the placebo group (10.2%) [11].

3.2 Methods and results

Although the risk of further fracturing is similar for low bone mineral density, among postmenopausal women aged 50 – 64 and 65 and older [12], there are few studies of the effects of anti-osteoporotic drugs on the 50 – 64 age group. Strontium ranelate has recently been shown to reduce vertebral fractures in postmenopausal women, aged 50 – 64, with a vertebral fracture in the most recent analysis of the SOTI, and the methods and results of this analysis are isesummarised in this section [13]. From the SOTI population, women aged 50 – 65 years were selected, and the mean age of the selected was 60 years. Most of the subjects (~ 80%) had ≥ 1 prevalent vertebral fractures, and the rest had a previous non-vertebral fracture. The T scores at the lumbar spine and femoral neck were ~ -3.6 and -2.5, respectively. All subjects received up to 1 g of elemental calcium and 400 – 800 IU of vitamin D, and were randomised to 2 g/day of strontium ranelate or placebo powder. Subjects could take their powder once (bedtime) or twice daily, but most preferred to take it once [7].

The primary endpoint was the incidence of subjects experiencing a new vertebral fracture, and this was determined by annual radiography of the spine. Over 3 years, the incidence of new vertebral fractures was 30% in the placebo group and 17% in the strontium ranelate group. The incidence of symptomatic vertebral fractures (vertebral fractures with back pain) was also reduced by strontium ranelate. There was no difference in incidence of non-vertebral fractures (~ 15%) in the placebo and strontium ranelate groups over 4 years.

Bone mineral density of the lumbar spine and proximal femur was measured by dual-energy X-ray absorptiometry at baseline and at 6 month intervals. After 4 years, the bone mineral density was reduced by -2.4 and -3.0% in the spine and femur of the placebo group, but increased by 15.8 and 7.1%, respectively, in the strontium ranelate group.

The incidence of adverse effects was similar in the placebo and treated groups. The initial report of SOTI showed that the only difference between the placebo and strontium ranelate group was an excess of diarrhoea in the strontium ranelate group (6.1%) over the placebo group (3.6%) at 1 year, but as this effect disappeared after 3 months [7], there was no excess after 4 years of treatment with strontium ranelate.

4. Expert opinion

4.1 Tibolone and breast cancer

When used as hormone replacement therapy, tibolone has variously been reported to increase the risk of breast cancer [2] or have no effect on the rates of breast cancer [3]. In the treatment of postmenopausal osteoporosis, tibolone decreased the incidence of breast cancer [6]. This difference may be related to the dose of tibolone, as a higher dose of tibolone has generally been used as hormone replacement therapy (2.5 mg) than in postmenopausal osteoporosis (1.25 mg).

4.2 Tibolone and stroke: should we be surprised?

In postmenopausal women, there is a small increased risk of stroke with estrogen and raloxifene [14], and in women with breast cancer, there is a small increased risk of stroke with tamoxifen [15]. Thus, it is probably not surprising that tibolone, which is chemically similar to these compounds, also causes a small increased risk of stroke. The mechanism underlying this increased risk of stroke with these compounds is not known, but if it is due to estrogen receptor stimulation, it will not be possible to separate the beneficial effects of estrogen-like drugs from their ability to increase the risk of stroke.

4.3 Is this the end of the development of tibolone for osteoporosis?

Tibolone is approved in 45 countries to prevent osteoporosis. LIFT has shown that tibolone increased the incidence of stroke. The authors of LIFT concluded that “In instances in which tibolone is approved for use, these potential risks and benefits and other effects should be weighed when considering the use of tibolone for the treatment of menopausal symptoms or fracture prevention”. With regard to osteoporosis, I would add ‘and compared with other medicines available for the treatment of osteoporosis’. For instance, zoledronic acid, the bisphosphonate used intravenously annually, has been shown to decrease the risk of fractures in postmenopausal osteoporosis without causing serious adverse effects [16]. Tibolone is comparable to raloxifene and oral bisphosphonates in decreasing fractures. As zoledronic acid causes a greater reduction in fractures than raloxifene and oral bisphosphonates [16], it is more potent than tibolone at reducing fractures. Thus, it seems to me that zoledronic acid should be preferred to tibolone for the treatment of postmenopausal osteoporosis. With our present knowledge, there seems no point in further development of tibolone for the treatment of postmenopausal osteoporosis.

4.4 Strontium and the importance of hip fractures

Hip fractures are the major cause of mortality and also cause morbidity in postmenopausal women with osteoporosis. Thus, it is important that drugs used in the treatment of osteoporosis are effective against both vertebral and non-vertebral fractures. Strontium is effective at preventing vertebral fracture, but has little or no effect on non-vertebral fractures. Alendronate, risedronate, zoledronic acid and estrogen have been shown to prevent hip fractures in postmenopausal women with osteoporosis [17]. Consequently, any of these drugs may be epreferable to strontium in the treatment of postmenopausal osteoporosis.

4.5 Conclusion

Recent major clinical outcomes trials have not established a role for either tibolone or strontium ranelate as a front-line treatment for osteoporosis in postmenopausal women.

Bibliography

1 . Lane NE. Epidemiology, etiology, and diagnosis of osteoporosis. *Am J Obstet Gynecol*2006;194:S3-11

2 . Beral V. Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet*2003;362:419-27

3 . Opatrny L, Dell'Aniello S, Assouline S, Suissa S. Hormone replacement therapy use and variations in the risk of breast cancer. *BJOG*2008;115:169-75

4 . Available from: http://www.worldhealth. net/news/strontium_breakthrough_ against_osteoporo

5 . Bjarnason NH, Bjarnason K, Haarbo J, et al. Tibolone: prevention of bone loss in late postmenopausal women. *J Clin Endocrinol Metab*1996;81:2419-22

6 . Cummings SR, Ettinger B, Delmas PD, et al. The effects of tibolone in old postmenopausal women. *N Engl J Med*2008;359:697-708

7 . Meunier P, Roux C, Seeman E, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *N Engl J Med*2004;350:359-68

8 . Marquis P, Roux C, de la Loge C, et al. Strontium ranelate prevents quality of life impairment in post-menopausal women with established vertebral osteoporosis. *Osteoporos Int*2008;19:503-10

9 . Reginster JW, Seeman E, De Vernejoul MC, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) Study. *J Clin Endocrinol Metab*2005;90:2816-22

10 . Roux C, Reginster YT, Fechtenbaum J, et al. Vertebral fracture risk reduction with strontium ranelate in women with postmenopausal osteoporosis is independent of baseline risk factors. *J Bone Miner Res*2006;21:536-42

11 . Reginster JY, Felsenberg D, Boonen S, et al. Effects of long-term strontium ranelate treatment of the risk of nonvertebral and vertebral fractures in postmenopausal osteoporosis: Results of a five-year, randomized, placebo-controlled trial. *Arthritis Rheum*2008;58:1687-95

12 . Siris ES, Brenneman SK, Miller PD, et al. Predictive value of low BMD for 1-year fracture outcomes is similar for postmenopausal women ages 50-64 and 65 and older: resultf for the National Osteoporosis Risk Assessment (NORA). *J Bone Miner Res*2004;19:1215-20

13 . Roux C, Fechtenbaum J, Kolta S, et al. Strontium ranelate reduces the risk of vertebral fracture in young postmenopausal women with severe osteoporosis. Ann Rheum Dis doi:10.1136/ard.2008.094516

14 . Mosca L, Grady D, Barrett-Connor E, et al. Effect of raloxifene on stroke and venous thromboembolism according to subgroups in postmenopausal women at increased risk of coronary heart disease. Stroke [Epub ahead of print]

15 . Bushnell C. The cerebrovascular risks associated with tamoxifen use. *Expert Opin Drug Saf*2005;4:501-7

16 . Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*2007;356:1809-22

17 . MacLean C, Newberry S, Maglione M, et al. Systematic review: comparative effectiveness of treatments to prevent fractures in

men and women with low bone density or osteoporosis. *Ann Intern Med*2008;148:197-213